ABC of diseases of liver, pancreas, and biliary system
Acute hepatitis

S D Ryder, I J Beckingham

Acute hepatic injury is confirmed by a raised serum alanine transaminase activity. The activity may be 100 times normal, and no other biochemical test has been shown to be a better indicator. Alkaline phosphatase and γ-glutamyltransferase activities can also be raised in patients with an acute hepatic injury, but their activites are usually proportionately lower than that of alanine transaminase.

Liver enzyme activity in liver disease

	Hepatitis	Cholestasis or obstruction	"Mixed"
Alkaline phosphatase	Normal	Raised	Raised
γ-glutamyltransferase	Normal	Raised	Raised
Alanine transaminase	Raised	Normal	Raised

Acute viral hepatitis

Hepatitis can be caused by the hepatitis viruses A, B, C, D, or E. The D and E forms are rare in the United Kingdom. A large proportion of infections with hepatitis viruses of all types are asymptomatic or result in anicteric illnesses that may not be diagnosed as hepatitis. Hepatitis A virus causes a typically minor illness in childhood, with more than 80% of cases being asymptomatic. In adult life infection is more likely to produce clinical symptoms, although only a third of patients with acute hepatitis A infections are jaundiced. Infections with hepatitis B and C viruses are also usually asymptomatic except in intravenous drug users, in whom 30% of hepatitis B infections are associated with jaundice.

In the preicteric phase, patients often have non-specific systemic symptoms together with discomfort in the right upper quadrant of the abdomen. An illness resembling serum sickness occurs in about 10% of patients with acute hepatitis B infection and 5-10% of patients with acute hepatitis C infection. This presents with a maculopapular rash and arthralgia, typically affecting the wrist, knees, elbows, and ankles. It is due to formation of immune complexes, and patients often test positive for rheumatoid factor. It is almost always self limiting, and usually settles rapidly after the onset of jaundice.

Rarely, patients with acute hepatitis B infection present with acute pancreatitis. Up to 30% of patients have raised amylase activity, and postmortem examinations in patients with fulminant hepatitis B show histological changes of pancreatitis in up to 50%. Myocarditis, pericarditis, pleural effusion, aplastic anaemia, encephalitis, and polyneuritis have all been reported in patients with hepatitis.

Common symptoms of acute viral hepatitis

- Myalgia
- Nausea and vomiting
- Fatigue and malaise
- Change in sense of smell or taste
- Right upper abdominal pain
- Coryza, photophobia, headache
- Diarrhoea (may have pale stools and dark urine)

Types and modes of transmission of human hepatitis viruses

	A	B	C	D	E
Virus type	Picorna-viridae	Hepadna-viridae	Flavi-viridae	Delta-viridae	Calci-viridae
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Mean (range) incubation period (days)	30 (15-50)	80 (28-160)	50 (14-160)	Variable	40 (15-45)
Mode of transmission:					
Orofaecal	Yes	Possible	No	No	Yes
Sexual	Yes	Yes	Rare	Yes	No
Blood	Rare	Yes	Yes	Yes	No
Chronic infection	No	Yes	Yes	Yes	No

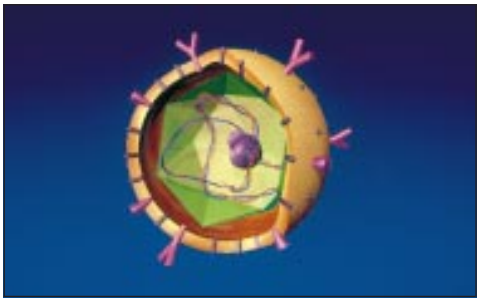
Other biochemical or haematological abnormalities seen in acute hepatitis

- Leucopenia is common ($< 5 \times 10^9$/l in 10% of patients)
- Anaemia and thrombocytopenia
- Immunoglobulin titres may be raised

Physical signs in viral hepatitis

Physical examination of patients before the development of jaundice usually shows no abnormality, although hepatomegaly (10% of patients), splenomegaly (5%), and lymphadenopathy (5%) may be present. Patients with an acute illness should not have signs of chronic liver disease. The presence of these signs suggests that the illness is either the direct result of chronic liver disease or that the patient has an acute event superimposed on a background of chronic liver disease—for example, hepatitis D virus superinfection in a carrier of hepatitis B virus.

A small proportion of patients with acute viral hepatitis develop a profound cholestatic illness. This is most common with hepatitis A and can be prolonged, with occasional patients remaining jaundiced for up to eight months.

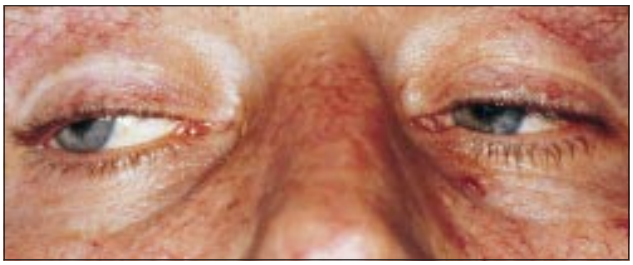


Structure of hepatitis B virus

Acute liver failure (fulminant hepatitis)

Death from acute viral hepatitis is usually due to the development of fulminant hepatitis. This is usually defined as development of hepatic encephalopathy within eight weeks of symptoms or within two weeks of onset of jaundice. The risk of developing fulminant liver failure is generally low, but there are groups with higher risks. Pregnant women with acute hepatitis E infection have a risk of fulminant liver failure of around 15% with a mortality of 5%. The risk of developing fulminant liver failure in hepatitis A infection increases with age and with pre-existing liver disease. Fulminant hepatitis B is seen in adult infection and is relatively rare.

The primary clinical features of acute liver failure are encephalopathy and jaundice. Jaundice almost always precedes encephalopathy in acute liver failure The peak of alanine transaminase activity does not correlate with the risk of developing liver failure. Prolonged coagulation is the biochemical hallmark of liver failure and is due to lack of synthesis of liver derived factors. Prolongation of the prothrombin time in acute hepatitis, even if the patient is clinically well without signs of encephalopathy, should be regarded as sinister and the patient monitored closely. Hypoglycaemia is seen only in fulminant liver disease and can be severe.



Disconjugate gaze due to cerebral oedema in jaundiced patient with fulminant hepatitis

The onset of confusion or drowsiness in a patient with acute viral hepatitis is always sinister

Diagnosis of acute hepatitis

Hepatitis A

Hepatitis A infection can be reliably diagnosed by the presence of antihepatitis A IgM. This test has high sensitivity and specificity. Occasional false positive results occur in patients with liver disease due to other causes if high titres of immunoglobulin are present, but the clinical context usually makes this obvious.

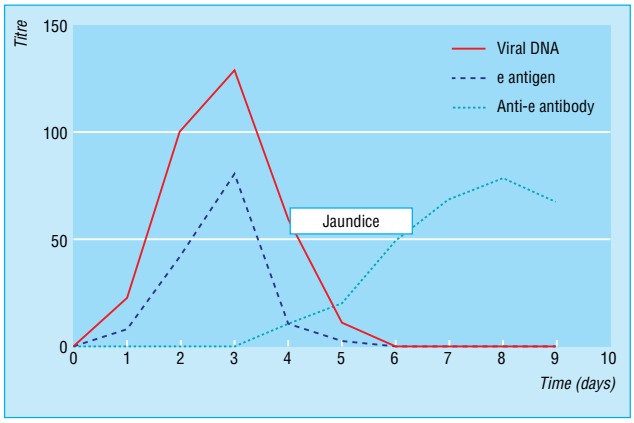
Hepatitis B

Hepatitis B infection is usually characterised by the presence of hepatitis B surface antigen. Other markers are used to determine if the virus is active and replicating, when it can cause serious liver damage.

In acute hepatitis B infection the serology can be difficult to interpret. Acute hepatitis develops because of immune recognition of infected liver cells, which results in T cell mediated killing of hepatocytes. Active regeneration of hepatocytes then occurs. As well as a cell mediated immune response, a humoral immune response develops; this is probably important in removing viral particles from the blood and thus preventing reinfection of hepatocytes. Because of the immune response attempting to eradicate hepatitis B virus, viral replication may already have ceased by the time a patient presents with acute hepatitis B, and the patient may be positive for hepatitis B surface antigen and negative for e antigen.

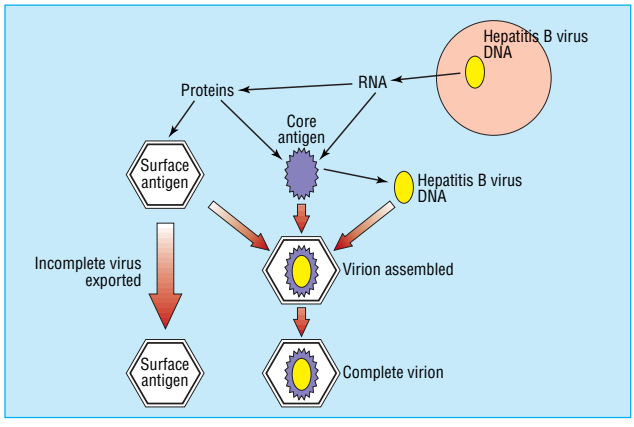
It is difficult in this situation to be certain that the patient had acute hepatitis B and that the serology does not imply past infection unrelated to the current episode. To enable a clear diagnosis, most reference centres now report the titre of IgM antibody to hepatitis B core antigen (IgM anticore). As core antigen never appears in serum, its presence implies an immune response against hepatitis B virus within liver cells and is a sensitive and specific marker of acute hepatitis B infection.

Rarely, the immune response to hepatitis B infection is so rapid that even hepatitis B surface antigen has been cleared from the serum by the time of presentation with jaundice. This may be more common in patients developing severe acute liver disease and has been reported in up to 5% of patients with fulminant hepatitis diagnosed by an appropriate pattern of antibody response.



Appearance of serological markers in acute self limiting hepatitis B virus infection

Replication of hepatitis B virus is assessed by measuring e antigen (a truncated version of the hepatitis B core antigen that contains the viral replication mechanism) and hepatitis B DNA



Mechanism of assembly and excretion of hepatitis B virus from infected hepatocytes

Hepatitis C

Screening tests for hepatitis C virus infection use enzyme linked immunosorbent assays (ELISA) with recombinant viral antigens on patients' serum. Acute hepatitis C cannot be reliably diagnosed by antibody tests as these often do not give positive results for up to three months.

Hepatitis C virus was the cause of more than 90% of all post-transfusion hepatitis in Europe and the United States. Before 1991, the risk of infection in the United Kingdom was 0.2% per unit of blood transfused, but this has fallen to 1 infection per 10 000 units transfused since the introduction of routine serological screening of blood donors. Acute hepatitis C infection is therefore now seen commonly only in intravenous drug users.

Antibodies to hepatitis C appear relatively late in the course of the infection, and if clinical suspicion is high, the patient's serum should be tested for hepatitis C virus RNA to establish the diagnosis.

Non-A-E viral hepatitis

Epstein Barr virus causes rises in liver enzyme activities in almost all cases of acute infection, but it is uncommon for the liver injury to be sufficiently severe to cause jaundice. When jaundice does occur in patients with Epstein Barr virus infection, it can be prolonged with a large cholestatic element. Diagnosis is usually relatively easy because the typical symptoms of Epstein Barr infection are almost always present and serological testing usually gives positive results. Cytomegalovirus can also cause acute hepatitis. This is unusual, rarely severe, and runs a chronic course only in immunosuppressed patients.

The cause of about 7% of all episodes of acute presumed viral hepatitis remains unidentified. It seems certain that other viral agents will be identified that cause acute liver injury.

Management of acute viral hepatitis

Hepatitis A

Most patients with hepatitis A infection have a self limiting illness that will settle totally within a few weeks. Management is conservative, with tests being aimed at identifying the small group of patients at risk of developing fulminant liver failure.

Hepatitis B

Acute hepatitis B is also usually self limiting, and most patients who contract the virus will clear it completely. All cases must be notified and sexual and close household contacts screened and vaccinated. Patients should be monitored to ensure fulminant liver failure does not develop and have serological testing three months after infection to check that the virus is cleared from the blood. About 5-10% of patients will remain positive for hepatitis B surface antigen at three months, and a smaller proportion will have ongoing viral replication (e antigen positive). All such patients require expert follow up (see article on chronic viral hepatitis).

Hepatitis C

Early identification and referral of cases of acute hepatitis C infection is important because strong evidence exists that early treatment with interferon alpha reduces the risk of chronic infection. The rate of chronicity in untreated patients is about 80%; treatment with interferon reduces this to below 50%.

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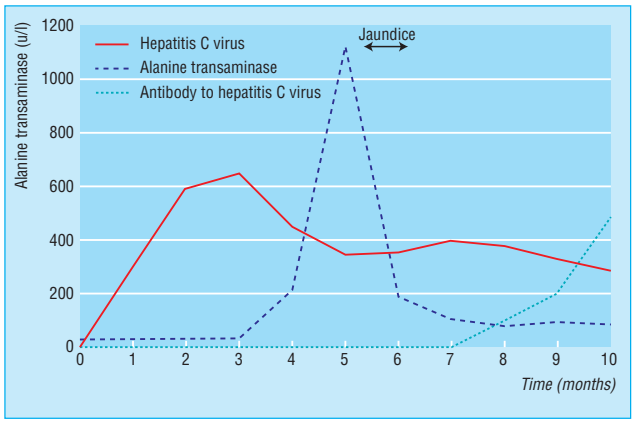


Appearance of hepatitis C virus RNA, antibodies to hepatitis C virus, and raised alanine transaminase activity in acute hepatitis C infection

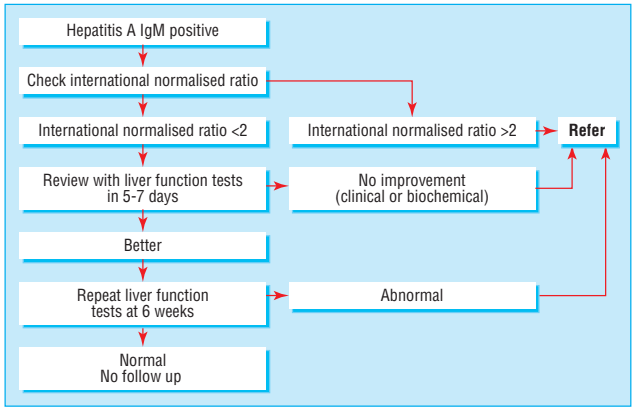
Hepatitis D and E infection

Hepatitis D

- Incomplete RNA virus that requires hepatitis B surface antigen to transmit its genome from cell to cell
- Occurs only in patients positive for hepatitis B surface antigen
- Usually confined to intravenous drug users in United Kingdom

Hepatitis E

- Transmitted by orofaecal route
- Produces an acute self limiting illness similar to hepatitis A
- Common in developing world
- High mortality in pregnant women



Management of acute hepatitis A infection in general practice

Summary points

- Symptoms of hepatitis are non-specific and often occur without the development of jaundice
- Serum alanine transaminase is the most useful screening test for hepatitis in general practice
- Hepatitis A rarely causes fulminant liver failure or chronic liver disease
- In the developed world, new cases of hepatitis C are mainly seen in intravenous drug users
- Most adults who contract hepatitis B virus clear the virus, with < 10% developing chronic liver infection

The ABC of diseases of liver, pancreas, and biliary system is edited by I J Beckingham, consultant hepatobiliary and laparoscopic surgeon, department of surgery, Queen's Medical Centre, Nottingham (Ian.Beckingham@nottingham.ac.uk). The series will be published as a book later this year.